Remarks

The Claims Amended

Applicant has amended claim 1 to recite that the vector comprises "a polynucleotide encoding a tag" to further clarify the claims. Support for this amendment can be found, for example, on p. 7, lines 7-13, of the specification. Applicant has also amended claim 1 to correct a typographical error: "the vector comprises" has been amended to "a vector comprises."

Applicant has also amended claim 2 and 3 to further clarify the invention.

Applicant has cancelled claim 10. The cancellation of claim 10 is without prejudice and without waiver of applicant's right to file for and obtain claims directed to any subject matter contained therein in divisional or continuing applications which claim priority from this application under 35 U.S.C. § 120.

Added claims 11-14 recite the subject matter in cancelled claim 10.

Added claims 15-16 recite part of the subject matter in original claim 3.

None of the foregoing amendments adds new matter.

Each of the Examiner's comments, objections and rejections is addressed below.

Priority

Applicant appreciates the Examiner's acknowledgement of applicant's claim of foreign priority. As requested by the Examiner, applicant has amended the specification to include the priority application data. Applicant has requested a certified copy of the European patent application. Applicant will file the certified copy of the European application as required by 35 U.S.C. 119(b) as soon as applicant receives the certified copy.

Claim Objections

The Examiner rejected claim 10 under 37 CFR 1.75(c) as being in improper form because multiple dependent claim 10 depends on a multiple dependent claim 3. Applicant has cancelled claim 10 and added claims 11-14. Claims 11-14 do not depend on a multiple dependent claim and are in proper form.

Accordingly, Applicant respectfully requests that the Examiner withdraw her 37 CFR 1.75(c) objection.

Claim Rejections - 35 U.S.C § 112

The Examiner rejected claims 1-3 under 35 U.S.C § 112, second paragraph, as being indefinite. Specifically, the Examiner stated that "the vector" in claim 1 lacks antecedent basis. Applicant has amended claim 1 such that the phrase "the vector" has proper antecedent basis.

The Examiner rejected claim 2 because claim 2 recites "polynucleotide according to claim 1" and claim 1 does not recite "polynucleotide." Applicant has corrected this inadvertent error. Amended claim 2 recites "the plurality of polynucleotides of claim 1."

The Examiner rejected claim 3 as being indefinite because it recites "preferably" and "most preferably." As requested by the Examiner, Applicant has amended the claim to recite the exact number of Fabs.

Accordingly, Applicant respectfully requests that the Examiner withdraw her 35 U.S.C § 112, second paragraph objection.

Claim Rejections - 35 U.S.C. § 102(b) - WO 94/05781

The Examiner argues that WO 94/05781 anticipates claims 1-3 and 10 of the present invention. In particular, the Examiner states that WO 94/05781 discloses "filamentous phage comprising heterologous polypeptides fused to filamentous phage coat protein membrane anchor and a heterodimeric receptor comprised of first and second receptor polypeptides." The Examiner also states that WO 94/05781 discloses "vectors comprising first and second cloning regions comprising restriction enzyme cleavage sites (e.g., figure 5), each cloning region has at the 5' end a ribosome binding site (RIBISI) (e.g., see figure 5), a first and second antibody variable regions (heavy chain fragment and light chain fragment in figure 5)." The Examiner concludes that WO 94/05781 "clearly anticipates the claimed invention." Applicant traverses.

One embodiment of the present invention is to create diverse phage display libraries of Fab fragments that may be directly screened. Further, the phage display libraries of the present invention are displayed using a single filamentous phage coat protein membrane anchor.

WO 94/05781 discloses "a filamentous phage comprising a) a heterologous polypeptide [i.e., a tag] fused to a first filamentous phage coat protein membrane anchor; and b) a heterodimeric receptor comprised of first and second receptor polypeptides [] fused to a second filamentous coat protein membrane anchor." WO 94/05781 p. 7, lines 4-10. WO 94/05781 states "that different heterologous polypeptides [i.e., the tags] can be engineered onto the surface of a single filamentous phage particle using either cpIII or cpVIII coat protein membrane anchors." See WO 94/05781 p. 1, lines 8-10. One problem associated with the system in WO 94/05781 is that the heterologous polypeptide (i.e., the tags) may not consistently be expressed with the heterodimeric receptor. See WO 94/05781 pp. 25-26. As such, the libraries of WO 94/05781 may not be directly screened for phages that express the heterodimeric receptor.

The present invention overcomes this problem. In the present invention, tags are defined as an "extension of the antibody Fab fragment, for example expressed at the carboxyterminus of the heavy chain" (p. 31, lines 24-26 of the specification). As such, the tags of the presently claimed invention do not require a separate filamentous phage coat protein membrane anchor as required by WO 94/05781. Consequently, the libraries of the presently claimed invention may be directly screened for phage that display Fab

fragments (since the tag is an extension of the antibody Fab fragment it is consistently expressed with the Fab fragment).

Accordingly, Applicant respectfully requests that the Examiner withdraw her 35 U.S.C. § 102(b) rejection and allow the presently claimed invention.

Claim Rejections - 35 U.S.C. § 102(b) - EP 844306 A1

The Examiner argues that EP 844306 A1 anticipates claims 1-3 and 10 of the present invention. In particular, the Examiner states that EP 844306 A1 (the '306 application) "teaches methods for producing members of specific binding pairs in recombinant host cells." The Examiner also states that the vector of the '306 application "comprises rbs at the 5' end of the cloning regions, restriction enzyme sites and first and second cloning regions comprising V_H and V_L antibody fragments, gIII at the 3' end of the second cloning region (e.g., see figure 27)." The Examiner concludes by stating "[t]he reference clearly anticipates the claimed invention." Applicant traverses.

The '306 application discloses five approaches that allegedly ameliorate the problem of making a large enough library that has an advantageous combination of V_H and V_L chains. See p.6, lines 12-48. Only the "fourth approach" discloses that "both chains are cloned into the same vector." See p. 6, lines 41-42 of the '306 application (in the present invention, two variable polynucleotides are cloned into one vector). The "fourth approach" also discloses that that "one of the chains which is already known to have desirable properties is kept fixed. A library of the complementary chain is inserted into the same vector. Suitable partners

for the fixed chain are selected following display on the surface of bacteriophage." See p. 6, lines 42-44 (emphasis added).

Unlike the '306 application, the present invention does not require that one know the desirable properties of one of the polynucleotides when cloning two polynucleotides into one vector. The present invention also does not require that either of the polynucleotides be kept fixed. Accordingly, unlike the '306 application, the present invention teaches that both the first and second polynucleotides are variable.

The Examiner cites to figure 27 of the '306 application as support that this reference anticipates the present invention. Figure 27 discloses the cloning of V_H and V_L antibody fragments into phagemid pHEN1. In figure 27, the DNA encoding the V_H and V_L antibody fragments is inserted into pHEN1 phagemid at the Sfi I and Not I site (i.e., one cloning region).

In the present invention, however, the vectors comprise a first and second cloning region. Each cloning region is flanked by a 5' ribosome binding site and a signal sequence. The first plurality of variable polynucleotides is cloned into the vector at the first cloning region. The second plurality of variable polynucleotides is cloned into the vector at the second cloning region. As such, the V_H and V_L sequences are randomly recombined in a single vector (see, e.g., p. 132, lines 2-8 of the specification). EP 844306 does not disclose this random recombination of the V_H and V_L sequences in a single vector.

Accordingly, Applicant respectfully requests that the Examiner withdraw her 35 U.S.C. § 102(b) rejection and allow the presently claimed invention.

Claim Rejections - 35 U.S.C. § 102(b) - US Patent 5,969,108

The Examiner argues that United States patent 5,969,108 (the '108 patent) anticipates claim 1-3 and 10 of the present invention. In particular, the Examiner states that the '108 patent discloses "a library of 10^{14} possible clones expressing the combination of H and L chain (refers to instant claim 3) (e.g., see column 6). The reference teaches vectors (or genetic packages) comprising from 5' to 3', rbs-enzyme cleavage site, vH-rbs-enzyme cleavage site-vL-N' terminus of gene III (e.g., see figure 45)." The Examiner concludes by stating "the reference clearly anticipates the claimed invention." Applicant traverses.

The '108 patent, like the '306 application, discloses five approaches that allegedly ameliorate the problem of making a large enough library that has an advantageous combination of V_H and V_L chains. See cols. 6-7. Only the "fourth approach" discloses that "both chains are cloned into the same vector." See col. 7, lines 6-8 of the '108 patent (in the present invention, two variable polynucleotides are cloned into one vector). The "fourth approach" also discloses that "one of the chains which is already known to have desirable properties is kept fixed. A library of the complementary chain is inserted into the same vector. Suitable partners for the fixed chain are selected following display on the surface of bacteriophage." See col. 7, lines 8-12 (emphasis added).

Unlike the '108 patent, the present invention does not require that one know the desirable properties of one of the polynucleotides when cloning two polynucleotides into one vector. The present invention also does not require that either of the polynucleotides be kept fixed. Accordingly, unlike the '108 patent, the present invention teaches that both the first and second polynucleotides are variable.

The Examiner cites to figure 45 of the '108 patent for support that it anticipates the present invention. Figure 45 is described in Example 39. Example 39 discloses that this method "opens the possibility to genetically select for stably associated Fv fragments with defined specificities from V gene libraries expressed in phages." See col. 90, lines 2-5 (emphasis added).

Unlike the '108 patent, the present invention does not require that the specificities of the polypeptides encoded by the polynucleotides be "defined." In fact, one of the goals of the invention is "to create a Fab library that is a valuable source of antibodies for many different targets." See p. 4, lines 23-27 of the specification.

Further, unlike the present invention, figure 45 of the '108 patent does not disclose a component for directly screening phage display libraries of variable first and second polynucleotides. In the presently claimed invention, a polynucleotide encoding a tag is also part of the vector that contains a first and second cloning region. Tags are defined in the specification as an "extension of the antibody Fab fragment, for example expressed at the carboxyterminus of the heavy chain" (p. 31, lines 24-26 of the specification). As such, unlike figure 45 of the '108 patent, the present

invention discloses a component for directly screening phage display libraries of variable first and second polynucleotides that are inserted into first and second cloning regions, respectively.

Accordingly, Applicant respectfully requests that the Examiner withdraw her 35 U.S.C. § 102(b) rejection and allow the presently claimed invention.

Claim Rejections - 35 U.S.C. § 102(e) - US Patent 6,172,197

The Examiner argues that United States patent 6,172,197 (the '197 patent) anticipates claim 1-3 and 10 of the present invention. In particular, the Examiner states that the '197 patent discloses "a library of 10^{14} possible clones expressing the combination of H and L chain (refers to instant claim 3) (e.g., see column 6). The reference teaches vectors (or genetic packages) comprising from 5' to 3', rbs-enzyme cleavage site, vH-rbs-enzyme cleavage site-vL-N' terminus of gene III (e.g., see figure 45)." The Examiner concludes by stating "the reference clearly anticipates the claimed invention." Applicant traverses.

The '197 patent, like the '306 application and the '108 patent, discloses five approaches that allegedly ameliorate the problem of making a large enough library that has an advantageous combination of V_H and V_L chains. See cols. 6-7. Only the "fourth approach" discloses that "both chains are cloned into the same vector." See col. 7, lines 16-18 (in the present invention, two variable polynucleotides are cloned into one vector). The "fourth approach" also discloses that "one of the chains which is already known to have desirable properties is kept fixed. A library of the

complementary chain is inserted into the same vector. Suitable partners for the fixed chain are selected following display on the surface of bacteriophage." See col. 7, lines 18-22 (emphasis added).

Unlike the '197 patent, the present invention does not require that one know the desirable properties of one of the polynucleotides when cloning two polynucleotides into one vector. The present invention also does not require that either of the polynucleotides be kept fixed. Accordingly, unlike the '197 patent, the present invention teaches that both the first and second polynucleotides are variable.

The Examiner cites to figure 45 of the '197 patent for support that it anticipates the present invention. Figure 45 is described in Example 39. Example 39 discloses that this method "opens the possibility to genetically select for stably associated Fv fragments with defined specificities from V gene libraries expressed in phages." See col. 88, lines 58-61 (emphasis added).

Unlike the '197 patent, the present invention does not require that the specificities of the polypeptides encoded by the polynucleotides be "defined." In fact, one of the goals of the invention is "to create a Fab library that is a valuable source of antibodies for many different targets." See p. 4, lines 23-27 of the specification.

Further, unlike the present invention, figure 45 of the '197 patent does not disclose a component for directly screening phage display libraries of variable first and second polynucleotides. In the presently claimed invention, a polynucleotide encoding a tag is also part of the vector that contains a first and second cloning region. Tags are

defined in the specification as an "extension of the antibody Fab fragment, for example expressed at the carboxyterminus of the heavy chain" (p. 31, lines 24-26 of the specification). As such, unlike figure 45 of the '197 patent, the present invention discloses a component for directly screening phage display libraries of variable first and second polynucleotides that are inserted into first and second cloning regions, respectively.

Accordingly, Applicant respectfully requests that the Examiner withdraw her 35 U.S.C. § 102(b) rejection and allow the presently claimed invention.

Conclusion

Should the Examiner feel that a telephone conference with applicant's representatives would assist the Examiner, she is invited to telephone the undersigned at any time.

For all the above reasons, Applicant requests favorable consideration and early allowance of the pending claims.

Respectfully submitted,

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